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P995 MYELOID NEOPLASMS-ASSOCIATED GENE VARIANTS IN 639 PATIENTS WITH POST-POLYCYTHEMIA VERA AND POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS: AN ANALYSIS OF THE MYSEC COHORT

Topic: 15. Myeloproliferative neoplasms - Biology & Translational Research

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Background: Polycythemia vera (PV) and essential thrombocythemia (ET) are myeloproliferative neoplasms evolving to post-PV (PPV-) and post-ET (PET-) myelofibrosis (MF), called secondary MF (SMF). In primary MF, knowledge on non-driver myeloid neoplasms-associated gene variants (M-GVs) influences clinical decision-making. In SMF, information on M-GVs is scant.

Aims: The primary aim was to assess the pattern of distribution of M-GVs, their correlations with SMF subtype and with driver mutations, in a large cohort of SMF patients studied by next generation sequencing (NGS).

Methods:

The study involved SMF patients of the MYSEC (*Myelofibrosis Secondary to PV and ET*) project. In 97% of cases, NGS were performed within one-year pre/post-SMF diagnosis. Characteristics of study cohort were described by standard statistic. Associations were investigated by Chi-square or Fisher exact test.

Results:

The clinical features of the 639 NGS-annotated patients entering the analysis are reported in **Table 1**.

Table 1. Characteristics of 639 NGS-annotated SMF.

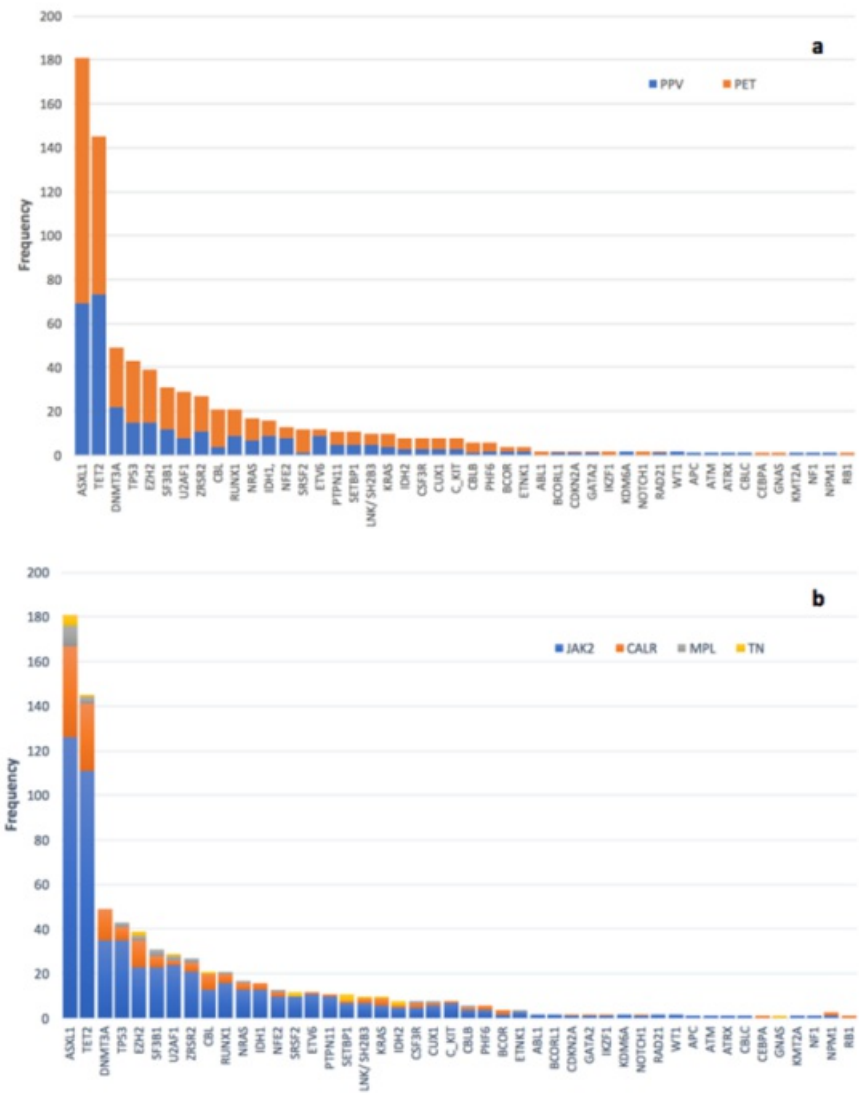
	SMF (639)	PPV-MF (290)	PET-MF (349)	*p*
Age at SMF (years), mean (SD)	62.2 (11.8)	63.2 (10.7)	61.4 (12.5)	0.17
Male gender, n (%)	323 (51)	151 (52)	172 (49)	0.48
***JAK2* mutated,** n (%)	477 (75)	290 (100)	187 (53)	
***CALR* mutated,** n (%)	125 (19)		125 (36)	
***MPL* mutated,** n (%)	24 (4)		24 (7)	
Triple negative, n (%)	13 (2)		13 (4)	
Hb (g/dl), mean (SD)	11.3 (2.1)	12.0 (2.1)	10.7 (1.9)	*<0.0001*
WBC (x10^9/l), mean (SD)	13.7 (12.7)	15.8 (13.9)	11.9 (11.3)	*<0.0001*
PLT (x10^9/l), mean (SD)	368.5 (248.4)	310.6 (211.6)	417.8 (266.4)	*<0.0001*
Blasts (%), mean (SD)	0.7 (1.9)	0.7 (1.6)	0.7 (2.1)	0.59
Constitut. symptoms, n (%)	259 (41)	134 (46)	125 (36)	*0.01*

A total of 198 (31%) patients did not harbor any M-GV, with no imbalance as for SMF subtype. Among the 441 (69%) with M-GVs, 223 (51%) had one, 137 (31%) two, 52 (12%) three, 23 (5%) four and 6 (1%) five or more. PPV-MF subjects reported more frequently one M-GV, while those with PET-MF at least three (*p=0.02*). Mean number of M-GVs was 1.4 per patient (range, 0-7). In detail, it was 1.2 (range, 0-4) and 1.5 (range, 0-7) per patient in PPV- and in PET-MF, respectively (*p=0.01*). The most frequent (≥5% of dataset) M-GVs involved: *ASXL1* (n=181, 41%), *TET2* (n=145, 33%), *DNMT3A* (n=49, 11%), *TP53* (n=43, 10%), *EZH2* (n=39, 9%), *SF3B1* (n=31, 7%), *U2AF1* (n=29, ~7%), *ZRSR2* (n=27, 6%), *CBL* and *RUNX1* (n=21 each, 5%). In PET-MF there was a significantly higher frequency of M-GVs in *ASXL1* (47% *vs* 34%, *p=0.01*), *SRSF2* (5% *vs* 1%, *p=0.01*), *U2AF1* (9% *vs* 4%, *p=0.04*) and *CBL* (7% *vs* 2%, *p=0.01*) compared to PPV-MF. The latter was significantly associated with *ETV6* alterations (5% *vs* 1% in PET-MF, *p=0.04*). As regards driver mutations, we found an association between "triple negative" status (TN) and M-GVs in *SETBP1* (38%, *p=0.002*), *IDH2* (25%, *p=0.02*), *EZH2* (25%, *p=0.05*),

and *SRSF2* (25%, *p=0.01*). **Figure 1** shows the frequency of M-GVs found in the MYSEC cohort, distinguished by SMF subtype (**a**) and driver mutations (**b**).

Image:

Figure 1. Pattern of distribution of myeloid neoplasms-associated gene variants in 441 patients with post-polycythemia vera and post-essential thrombocythemia myelofibrosis, distinguished by diagnosis (a) and driver mutation status (b).



Summary/Conclusion:

Among 639 NGS-annotated SMF cases, 69% presented at least one M-GV with a mean of 1.4 per patient. Overall,

the most frequent (≥10%) M-GVs were in *ASXL1, TET2, DNMT3A* and *TP53* genes. Different pathways of progression among PPV- and PET-MF have been disclosed. PPV-MF showed an increased rate of *ETV6* alterations, opening the question of possible predisposing genetic factors. TN cases clustered with specific M-GVs, potentially targetable (*IDH2*). This is the first study exploring the mutational landscape of a wide cohort of SMF patients, paving the way for further investigations on the topic.